CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216157Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 121691

MEETING PRELIMINARY COMMENTS

Global Blood Therapeutics, Inc.
Attention: Linda Yokoshima
Senior Director, Regulatory Affairs
181 Oyster Point Blvd.
South San Francisco, CA 94080

Dear Ms. Yokoshima:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for voxelotor.

We also refer to your correspondence, dated and received February 2, 2021, requesting a meeting to discuss submission of both an efficacy supplement and New Drug Application (NDA).

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at 301-796-7775.

Sincerely,

{See appended electronic signature page}

May Zuwannin
Regulatory Project Manager
Nonmalignant Hematology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: March 30, 2021, 1:00 PM – 2:00 PM (ET)
Meeting Location: Teleconference

Application Number: 121691
Product Name: voxelotor
Indication: Sickle Cell Disease
Sponsor Name: Global Blood Therapeutics, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetics Act

FDA ATTENDEES (tentative)

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Ellis Unger, MD, Director

OCHEN, Division of Nonmalignant Hematology (DNH)
Ann Farrell, MD, Director
Albert Deisseroth, MD, PhD, Supervisory Associate Director
Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling
Tanya Wroblewski, MD, Associate Director of Therapeutic Review
Carrie Diamond, MD, Clinical Reviewer
Patricia Oneal, MD, Clinical Reviewer
Julie Weisman, MD, Clinical Reviewer

Office of Biostatistics (OB), Division of Biometrics IX
Yeh-Fong Chen, PhD, Statistical Team Lead
Lola Luo, PhD, Statistical Reviewer

Office of Clinical Pharmacology (OCP)
Sudharshan Hariharan, PhD, Clinical Pharmacology Team Lead
Snehal Samant, PhD, Clinical Pharmacology Reviewer

Office of New Drug Products (ONDP)
David J. Claffey, PhD, Branch Chief (Acting)
Ali Mohamadi, PhD, Quality Reviewer

Office of Regulatory Operations (ORO)
Charlene Wheeler, MSHS, Chief, Project Management Staff
May Zuwannin, Regulatory Project Manager

SPONSOR ATTENDEES

Name	Title
Ted W. Love, MD	Chief Executive Officer
Kim Smith-Whitley, MD	Incoming Executive Vice President and Head of Research and Development
Rajiv Patni, MD	Chief Medical Officer
Jonathan Sorof, MD	Senior Vice President, Medical Affairs
Nazila Habibizad	Senior Vice President, Operations
Sandeep Kumar, PhD	Vice President, Regulatory Affairs
Deborah Arrindell, MD, MPH, JD	Vice President, Pharmacovigilance
Michael Conner, DVM	Vice President, Nonclinical Development
Patrick Yue, MD	Executive Director, Clinical Science
David Gao, PhD	Executive Director, Technical Operations
Linda Yokoshima	Executive Director, Regulatory Affairs
Margaret Tonda, PharmD	Senior Director, Clinical Science
Carla Washington, PhD	Senior Director, Clinical Pharmacology
Karen Jacobs, MSN, RN	Senior Director, Pharmacovigilance
Sarah Gray, PhD	Senior Director, Biostatistics
Paul Talierco	Senior Director, Regulatory Affairs, CMC
Sandy Dixon, MS	Director, Biostatistics
Shaimaa Shafie	Director, Regulatory Affairs

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the teleconference scheduled for March 30, 2021, 1:00 PM – 2:00 PM (ET), between Global Blood Therapeutics, Inc. and the Division of Nonmalignant Hematology. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Voxelotor is a first in class small-molecule HbS polymerization inhibitor. Oxbryta (voxelotor) was approved by the United States (US) Food and Drug Administration on November 25, 2019, for the treatment of Sickle Cell Disease (SCD) in adults and

pediatric patients 12 years of age and older. Given the unmet medical need in patients ≤12 years of age, GBT plans to submit an efficacy supplement to NDA 213137 based on efficacy, safety, and PK data from Part C of the ongoing phase 2a open-label Study GBT440-007 to expand the age range indicated for voxelotor to ≥4 years of age.

The purpose of this meeting is to discuss the proposal for the content of the planned efficacy sNDA and the adequacy of the data package to support the expansion of the indicated age range for voxelotor to ≥4 years of age and inclusion of other relevant updates to the United States Prescribing Information (USPI). The sponsor is also requesting feedback regarding the planned NDA to support a new dispersible tablet dosage form intended for pediatric patients <12 years of age.

2.0 DISCUSSION

Question 1: (b) (4)

1. (b) (4)
2.

We do not agree that (b) (4) in patients aged 12 years and older as described in the meeting package (b) would be sufficient to provide confirmatory evidence of the clinical benefit of voxelotor.

We await the completion of Part C, Study GBT-007, which may support an accelerated approval in patients age 4 to 12. If successful, the results from Study GBT440-032 could provide confirmatory evidence of clinical benefit for patients in both populations (4 to 12; 12 to adult).

Question 2: Does the Agency agree that the proposed content and format of the efficacy supplement support lowering the indicated age range for Oxbryta from ≥ 12 years of age to ≥ 4 years of age?

FDA Response: Please see response to Question 1.

The Agency agrees with your proposal of using new clinical relative bioavailability and bioequivalence data from Studies GBT440-00113 and GBT440-0114, the additional DDI clinical pharmacology study, and efficacy and safety data from your pediatric study GBT440-007 Part C to support the efficacy supplement. The 72-week data from GBT440-031 can provide supportive safety and efficacy data (durability of hemoglobin response and measures of hemolysis). Whether any additional claims can be made based on the 72-week data (durability of hemoglobin response and measures of hemolysis) from Study GBT440-031 will be a review issue. The exploratory analyses from Study GBT440-031 are not sufficient to support any labeling claims in terms of clinical benefit.

Question 3: Does the Agency agree with the proposed scope of the revisions to the USPI?

FDA Response: It is premature to discuss labeling revisions based upon your proposed application.

Question 4: Does the Agency agree with GBT's approach to establish the proposed commercial manufacturing process control strategy for dispersible tablet based on a combination of manufacturing experience with clinical lots of dispersible tablet and prior knowledge from the well-characterized commercial manufacturing process of Oxbryta 500 mg tablets?

FDA Response: Based on the information provided in the meeting background information package, GBT's approach to establish the proposed commercial manufacturing process control strategy for the proposed dispersible tablets based on a combination of manufacturing experience with clinical lots of dispersible tablets and prior knowledge from the well-characterized commercial manufacturing process of voxelotor 500 mg tablets appears reasonable. The adequacy of the available information will be determined at the time of review of the NDA.

Question 5: A new NDA will be submitted for a new dosage form, Oxbryta (voxelotor) dispersible tablet, for pediatric patients. GBT intends to submit a Letter of Authorization to cross reference NDA 213137. In addition, GBT plans to include Section 1.4.4 Cross-reference to Previously Submitted Information as a Letter specifying the sections that will be cross-referenced to NDA 213137. Does the Agency agree with this proposal?

FDA Response: The Agency agrees with the proposal.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 23, 2021, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

plans that would cause your application to trigger PREA, your exempt status would change.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[2]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[3]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

[2] http://www.fda.gov/ectd
[3] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

METANUJ ZUWANNIN
03/26/2021 04:21:36 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 121691

MEETING MINUTES

Global Blood Therapeutics, Inc.
Attention: Martine Kraus, PhD
Vice President, Regulatory Affairs and Quality Assurance
400 East Jamie Court, Suite 101
South San Francisco, CA 94080

Dear Dr. Kraus:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GBT440.

We also refer to the meeting between representatives of your firm and the FDA on July 26, 2016. The purpose of the meeting was to discuss your Phase 3 study plan and proposed registration plan for GBT440 for the treatment of sickle cell disease (SCD) in adult and pediatric patients.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jessica Boehmer, Senior Regulatory Project Manager at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Acting Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	July 26, 2016; 3:00 PM – 4:00 PM ET
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 121691
Product Name:	GBT440
Indication:	For the treatment of Sickle Cell Disease
Sponsor/Applicant Name:	Global Blood Therapeutics, Inc.
Meeting Chair:	Nicole Gormley, MD
Meeting Recorder:	Jessica Boehmer, MBA

FDA ATTENDEES

Office of Hematology and Oncology Products/Division of Hematology Products
Ann Farrell, MD, Director
Edvardas Kaminskas, MD, Deputy Director
Nicole Gormley, MD, Team Leader, Acting
Hyon-Zu Lee, PharmD, Clinical Reviewer
Virginia Kwitkowski, MS, ACNP-BC, Clinical Team Leader, Associate Director for Labeling
Rachel Ershler, MD, Clinical Reviewer
Rosanna Setse, MD, Clinical Reviewer
Jessica Boehmer, MBA, Senior Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V
Lei Nie, PhD, Statistical Team Leader
Kyung Y. Lee, PhD, Statistical Reviewer

Division of Hematology Oncology Toxicology
Christopher Sheth, PhD, Supervisory Pharmacologist
Pedro Del Valle, PhD, Pharmacologist

Office of Clinical Pharmacology
Stacy Shord, PharmD, Clinical Pharmacology Team Leader
Guoxiang (George) Shen, PharmD, Clinical Pharmacology Reviewer

Lily (Yeruk) Mulugeta, PharmD, Pharmacometrics Reviewer

Office of the Commissioner / Office of Minority Health
Jonca Bull, MD, Director

Office of New Drugs (OND) / Immediate Office (IO) / Rare Diseases Program
Lucas Kempf, MD, Medical Officer

OND / IO / Clinical Outcomes Assessment Staff
Selena Daniels, PharmD, Team Leader

Office of Surveillance and Epidemiology
Sarah Harris, PharmD, RPh, Project Management Team Leader

SPONSOR ATTENDEES

Global Blood Therapeutics
Ted Love, MD, Chief Executive Officer
Eleanor Ramos, MD, Chief Medical Officer
Ken Bridges, MD, Vice President, Medical Affairs
Josh Lehrer, MD, Senior Director, Clinical Sciences
Margaret Tonda, PharmD, Senior Director, Clinical Sciences
Carla Washington, PhD, Senior Director, Clinical Pharmacology
Jitendra Ganju, PhD, Vice President, Biometrics
Athiwat Hutchaleelaha, PhD, Vice President, Drug Metabolism and Pharmacokinetics
(b) (4), Independent Pharmacology and Toxicology Consultant
Martine Kraus, PhD, Vice President, Regulatory Affairs and Quality Assurance

(b) (4) Clinical Pharmacology Consultant (by telephone)

(b) (4)

1.0 BACKGROUND

The purpose of this meeting is to discuss the Phase 3 study plan and proposed registration plan for GBT440 for the treatment of sickle cell disease (SCD) in adult and pediatric patients.

GBT440 is an orally bioavailable hemoglobin (Hb) modifier. GBT440 is under clinical development for the treatment of SCD (IND 121691). A Phase 1/2 study evaluating GBT440 in adults (Study GBT440-001) is ongoing and several clinical pharmacology studies (including Studies GBT440-002, GBT440-003, GBT440-004, GBT440-005, and GBT440-008) are complete or are in progress at this time. Also in progress is a Phase 2a study in adolescents (Study GBT440-007).

GBT is evaluating GBT440 for the treatment of sickle cell disease (SCD) under IND 121691 (Division of Hematology Products). GBT440 for SCD has been granted fast track (October 7, 2015) designation and orphan product designation (December 29, 2015).

FDA sent Preliminary Comments to Global Blood Therapeutics, Inc. on July 19, 2016.

2. DISCUSSION

Preamble:

As currently proposed, your development plan has significant deficiencies. The Agency has the following concerns/questions which we hope to begin to address during the scheduled meeting:

- **The impact that your product will have on the clinical course of patients with sickle cell disease is not clear.**
- **The proposed** (b) (4) **is not a measure of clinical benefit and has not been demonstrated to be a surrogate that is reasonably likely to predict clinical benefit.**
- **You have proposed for your phase 3 trial a patient population that has relatively mild disease (≥ 1 VOC in the preceding year). When evaluating diseases that have a relatively mild phenotype, there is a risk that it will be possible to demonstrate only minimal improvement as a result of the intervention. You should consider evaluating a more severely affected patient population which will make possible the measurement of an effect of therapy that is greater in magnitude. The same suggestion can be made for your** (b) (4) **development.**
- **In the phase 1 study, there were several events of sickle cell anemia with crisis that occurred after discontinuation of GBT-440 or during treatment holds. These events are concerning and no explanation has been provided for these events. The effect of GBT-440 on erythropoietin, specifically the increases noted with higher dose levels, is also of concern and requires further explanation.**
- **Please also explain why the Hgb rise is minimal, while hemolysis is decreased.**

2.1. Clinical Questions

GBT has the following questions related to clinical development and statistical considerations:

Question 1: Does the Agency agree that the data from the ongoing Phase 1/2 study (GBT440-001) of the PK, safety, and treatment response of GBT440 in healthy subjects and subjects with SCD support further evaluation of GBT440 in the proposed Phase 3 study GBT440-031?

FDA Response to Question 1: **No. Before commencing your Phase 3 trial, address the following:**

- **Your observed dose response data indicate response to treatment may plateau at dose of 500 to 700 mg for reduction in % of irreversible sickle cells and LDH. In addition, the erythropoietin data show inverse U-shaped dose-response**

relationship between GBT440 dose and erythropoietin levels, indicating a potentially deleterious effect at high doses of GBT440. Therefore, there is no clear justification for the proposed 900 mg once daily dose. In order to assess whether there are Cmax related toxicities, you will need to evaluate the data from 900 mg once daily dose in the ongoing Phase 1 trial (Study GBT440-001) before using this dose in a pivotal trial.

- **Your dose-response analyses should also include safety endpoints. Your meeting package indicates adverse events including rash, gastrointestinal adverse effects (diarrhea, abdominal pain, etc.), and sickle cell anemia with crisis were observed. We noticed that in your ongoing and completed trials, 8 subjects in the treatment arm experienced sickle cell anemia with crisis; since GBT440 is intended for the treatment of sickle cell anemia, please explain this seemingly contradictory finding.**
- **In order to assess the therapeutic benefit of GBT440 at multiple dose levels, we recommend you evaluate two dose levels in your planned Phase 3 trial.**
- **Assess safety of GBT440 in adolescent patients using data from your ongoing trial (study GBT440-007) and add an additional cohort of 900 mg.**

Discussion:

The Sponsor provided background on the safety and activity observed with GBT-440 thus far. The Sponsor also presented a revised proposal for a pivotal trial, which is designed as a phase 2/3 trial (see attached Sponsor slides). The phase 2 portion of the trial will enroll 3 dose cohorts (a placebo arm and two GBT-440 dose levels). The phase 3 portion will compare a placebo arm with the dose selected from phase 2. The proposed primary endpoint is (b) (4). The Agency stated that while it is advisable to conduct a phase 2 trial before initiating a pivotal phase 3 trial, the specific details of their proposed phase 2/3 will need to be carefully considered and discussed with the Agency before initiation. Specific concerns with the proposed design include how the (b) (4) will be validated in the phase 2 portion, carryover of some patients from the phase 2 portion to the phase 3 portion, and other concerns pertaining to the analysis of the phase 2 to inform the phase 3 trial.

With regards to the endpoint used, the Agency reiterated that the Sponsor should carefully consider the clinical benefit measurement(s) they expect their product to affect. This information will inform the choice of an appropriate trial endpoint for their pivotal trial. The Agency stated that it may be acceptable to use the (b) (4). The Agency encouraged the Sponsor to continue development of their biomarker evaluations, as this may provide important supportive information. Please see post-meeting minutes below.

Question 2: The dose to be evaluated in Phase 3 study GBT440-031 was selected based on treatment response and safety data from Study GBT440-001 and PK/pharmacodynamic (PK/PD)modelling/simulation. The dose GBT440 900 mg was selected to achieve Hb modification in the range of 10% to 30%, an efficacy target which is genetically validated for

fetal hemoglobin. Does the Agency agree with the rationale provided and the dose GBT440 900 mg proposed for evaluation in Study GBT440-031?

FDA Response to Question 2: **No. Provide a final summary table of safety and efficacy results of the multiple dosing cohorts from the GBT440-001 and GBT440-007 trials when available with the justification of the proposed dose (900 mg once daily) for the phase 3 trial (GBT440-31) that includes the adolescent population (12 to <18 years of age).**

No, instead of using one endpoint (Hb modification), your dose selection should be based on all the evaluated PD markers (Hb increase, reticulocyte count, sickle cell reduction, LDH reduction, etc.). These PD markers indicate that maximum drug effect may be achieved at doses of 500 to 700 mg; therefore, there is no clear justification for the selected dose of 900 mg once daily. Also see response to Question 1.

Discussion:

The Sponsor provided additional safety data observed with 90 days GBT-440 treatment at 900 mg to support the safety of selected doses of 900 mg and 1500 mg. The Sponsor provided one subject's dose-response (biomarker) profiles during dose-adjustment to support the use of Hb occupancy >20% in selection a dose that may provide clinical benefit in patients with SCD. The Sponsor also clarified that pre-dose concentrations (Cmin) of GBT440 were used in the calculation of Hb occupancy. The Agency stated that the dose-response analyses are not conclusive due to the small number of subjects in each cohort, significant PK variability, and the narrow dose range investigated. The Agency recommended the Sponsor conduct model-based exposure-response analyses to potentially overcome the above issues and to support the Phase 2 dose selection. Additionally, the Agency recommended that the Sponsor include justification for the selected target Hb occupancy and a description of how Hb occupancy is determined in patients to support the Phase 2 dose selection. The Agency also suggested the Sponsor to consider alternative dosing regimens such as twice a day dosing regimen if high Cmax leads to significant adverse events. The Sponsor agreed to provide these analyses and information with the protocol for the proposed Phase2/3 trial.

Question 3: Does the Agency agree with the design of the proposed Phase 3 study (Study GBT440-031) including the study population (adults and adolescents), sample size, planned evaluations of efficacy and safety, plan for dose reduction/study drug discontinuation, and study duration?

FDA Response to Question 3: **No. Your proposed** (b) (4) **. You have not provided any information/justification regarding the thresholds you have chosen and have not provided evidence that this** (b) (4) **is predictive of clinical benefit in sickle cell disease.**

Discussion:

See discussion captured for Questions 1 and 2 and post-meeting note.

Question 4: Does the Agency agree with the proposed monitoring plan for Study GBT440-031 including safety assessments performed at each study visit, frequency of visits and the plan for Data Safety Monitoring Board (DSMB) oversight of the study?

FDA Response to Question 4: **Yes.**

Discussion:

No discussion occurred.

Question 5: Does the Agency agree with the proposed (b) (4)

FDA Response to Question 5: **No. See response to Question 3.**

Discussion:

No discussion occurred.

Question 6: Does the Agency agree with the key secondary endpoint (b) (4) and the proposed alpha-controlled secondary endpoints and multiple testing procedures as defining an improvement in clinical outcomes in Phase 3 Study GBT440-031?

FDA Response to Question 6: **Your proposed endpoints of (b) (4) the rate of VOC are measurements of clinical benefit and could be acceptable endpoints for registrational purposes depending on how they are defined and the validation of your (b) (4). See also response to Question 3.**

(b) (4)

(b) (4)

Discussion:

See discussion captured for Questions 1 and 2 and post-meeting note.

Additional Comment:

(b) (4)

Question 7: Does the Agency agree that the proposed Phase 3 study (Study GBT440-031), if positive for both the primary and key secondary (b) (4) endpoints, together with confirmatory evidence from the Phase 2 program would together provide adequate evidence of effectiveness to support review of an NDA for this fast track and orphan drug designated therapy, according to the FDAMA 115 requirement of a single adequate and well controlled study together with confirmatory evidence?

FDA Response to Question 7: **No. See response to Question 3.**

Discussion:

No discussion occurred.

Question 8: Does the Agency agree that the proposed NDA safety database in adult and pediatric subjects is adequate to support an NDA for GBT440 for the treatment of SCD in adult patients and pediatric patients (b) (4)?

[1] Guidance for Industry: Electronic Source Data in Clinical Investigations
(http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf)

FDA Response to Question 8: **Your proposal for the safety database appears acceptable at this time. However, this will be a review issue.**

Discussion:

No discussion occurred.

Question 9: Does the Agency agree that the proposed plan to study GBT440 in adolescents and in adults with SCD in the proposed Phase 3 efficacy and safety study and to conduct single-dose PK and longer-term safety and PK/PD bridging studies (b) (4)

FDA Response to Question 9: **The overall plan for pediatrics is not unreasonable.** (b) (4)

Discussion:

No discussion occurred.

Question 10: Does the Agency agree that available data in adults and forthcoming data in adolescent subjects (from Part B of Study GBT440-007 and planned Study GBT440-031) support dosing in children < 12 years of age on the schedule described in Section 6 of the Meeting Background Package?

FDA Response to Question 10: **Yes, the review of the adult and adolescent data may allow dosing of GBT440 in your planned single and multiple dose pediatric PK studies.**

Discussion:

No discussion occurred.

Question 11: Does the Agency agree that the proposed Phase 2 study (Study (b) (4)), if positive in outcome for safety and efficacy across the primary endpoint, will support a request for breakthrough designation? Does the Agency have any comments about the study design?

FDA Response to Question 11: (b) (4)

(b) (4)

Discussion:

The Agency stated that as development continues with GBT-440 and the sponsor has preliminary clinical evidence suggesting that GBT-440 may demonstrate a substantial improvement on a clinically significant endpoint over available therapy, the Agency would be willing to provide preliminary breakthrough designation request advice before official submission of the breakthrough designation request.

2.2. Clinical Pharmacology Questions

GBT has the following specific questions related to clinical pharmacology:

Question 12: Apart from the data requirements for the new tablet formulation with which the proposed Phase 3 study is planned to be conducted, does the Agency agree that the proposed clinical pharmacology program supports initiation of the planned Phase 3 study (GBT440-031) and supports the submission of an NDA for GBT440 for SCD?

FDA Response to Question 12: **No. Although the proposed clinical pharmacology program appears to be adequate to support the initiation of the planned Phase 3 study, if a dosing regimen higher than 600 mg QD is selected for the Phase 3 trial, additional DDI assessment for GBT440 as an inhibitor should be conducted at the Phase 3 study dose to support the submission of the NDA so that risk of DDI is not underestimated.**

Discussion:

No discussion occurred.

Question 13: Does the Agency agree that measuring the concentration of GBT440 in blood and plasma in the proposed Phase 3 study is adequate and that measuring of the minor active metabolite representing 2.5% and 2.75% of the total exposures (AUC) in blood and plasma, respectively, is not necessary?

FDA Response to Question 13: **Yes, we agree.**

Discussion:
No discussion occurred.

Question 14: Does the Agency agree with the use of population PK analysis to evaluate the effects of gender, age, and other covariates on the disposition of GBT440?

FDA Response to Question 14: **Yes, we agree.**

Discussion:

No discussion occurred.

Question 15: Does the Agency agree that the electrocardiogram (ECG) exposure/response QTc analysis of data from Study GBT440-001 provided under separate forthcoming submission to IND 121691 (serial number to be assigned) exclude a QTc effect of concern and that therefore a thorough QTc study is not required to support an NDA for GBT440 for SCD?

FDA Response to Question 15: **More information is needed to respond to this question.**

Discussion:

No discussion occurred.

Question 16: Does the Agency agree that the planned drug-drug interaction (DDI) studies are adequate to support an NDA for GBT440 for use in the treatment of SCD?

FDA Response to Question 16: **No. See response to Question 12.**

Discussion:

No discussion occurred.

Question 17: Does the Agency agree that the planned studies in special populations are adequate to support an NDA for GBT440 for use in the treatment of SCD?

FDA Response to Question 17: **No. Please provide rationale why subjects with severe hepatic impairment are excluded in the planned hepatic impairment study.**

Additional Clinical Pharmacology Comments:
Regarding the proposed Phase 3 study GBT440-031:

- **Please include the sampling time points for PK and 12-lead ECG assessment.**
- **Please include exclusion criteria for bilirubin so that subjects with moderate and severe hepatic impairment will be excluded.**
- **Patients should be advised to avoid taking GBT440 with high-fat meals.**

Discussion:

No discussion occurred.

2.3. Nonclinical Pharmacology/Toxicology Questions

GBT has the following specific question related to nonclinical pharmacology/toxicology:

Question 18: Does the Agency agree that the nonclinical data package available at the time of the start of the Phase 3 study (including the proposal for provision of data from the chronic

studies as outlined in Section 7.1.3.4) is adequate to support the proposed Phase 3 study (GBT440-031)?

FDA Response to Question 18: **The Agency is concerned with the findings from the ongoing 26-week rat and 39-week monkey studies that were summarized in the meeting package, specifically the moribundity/mortality that apparently began occurring at around 90 days of dosing at human equivalent doses that are lower than the proposed dose for Phase 3. We note that the safety margins based on AUC from 13-week monkey study are 2.1 and 1.8 in males and females, respectively. Safety margins based on body surface from 13-week monkey study area appear to be <1 (30 mg/kg in monkeys represents a HED of 9.73 mg/kg or 681.1 mg total per dose for a 70 kg patient compared to 900 mg dose for Phase 3).**

The Agency expects that audited draft reports with signed anatomic pathology reports, or finalized study reports for the 26-week and 39-week repeat-dose studies in rats and monkeys, respectively, will be made available for FDA review before extending dosing in the Phase 3 clinical trial beyond 3 months.

Discussion:

No discussion occurred.

Question 19: Does the Agency agree that the nonclinical data package, including the standard battery of reproductive and chronic toxicity studies and the carcinogenicity study in the transgenic mouse (with submission of 2-year carcinogenicity data following the NDA action date) is adequate to support an NDA for GBT440 for SCD?

FDA Response to Question 19: **The nonclinical data package appears reasonable to support an NDA. The adequacy of studies scheduled for future completion will be a review issue.**

Discussion:

No discussion occurred.

Question 20: Does the Agency agree that a definitive juvenile toxicity study is not required as a stepwise approach to dosing in children is proposed in Section 6 (Plan for Evaluation of GBT440 in Pediatric Population – see Figure 22) of the background package?

FDA Response to Question 20: **Yes, we agree.**

Discussion:

No discussion occurred.

2.4. Regulatory Questions

GBT has the following specific question related to regulatory activities:

Question 21: Although orphan drug designation has been granted for GBT440 for the treatment of SCD and the NDA will be exempt from PREA (FDCA 505B) requirements [including the 210-day review of a Pediatric Study Plan (PSP)], (b) (4)

FDA Response to Question 21: **No, the Agency is not in agreement with your proposed development plan.**

Discussion:

No discussion occurred.

Question 22: Does the Agency agree that the proposed pediatric study plan will support a rare pediatric disease priority review voucher in case the rare pediatric disease priority review voucher provision is renewed and all other criteria are met?

FDA Response to Question 22: **Because the current program expires on September 30, 2016, we cannot address this question.**

Discussion:

No discussion occurred.

Question 23: Does the Agency agree that the separate EOP2/CMC-specific meeting to discuss chemistry and manufacturing considerations for GBT440 may be requested as a Type B meeting?

FDA Response to Question 23: **Yes.**

Discussion:

No discussion occurred.

Additional comments for your current design and analysis plan:

- **The efficacy endpoint analyses population should be intent-to–treat (ITT) population which includes all randomized subjects.**

- **In your current analysis plan, if the sample size in any strata is less than 5, the primary analysis (CMH test) will be replaced with Fisher's exact test. We note that CMH test works well with sparse data and recommend that you continue to use CMH test with pre-specified rules to combine extremely sparse data, e.g. strata with sample size less than 2. Fisher's exact test may be used as a sensitivity analysis.**

- **Please include age (adolescent versus adult) as a stratification factor.**

- **You noted that for the primary efficacy endpoint, missing data at week 24 will be imputed with data closest to the Week 24 visit but after Week 17 visit. We recommend the sensitivity analysis that considers missing Week 24 data as non-responders. Please also clarify whether data post Week 24 would be used for imputation.**

- **We recommend the sensitivity analysis considering subjects with rescue medications as non-responders for the primary endpoint.**

- **We note that missing at random (MAR) assumption you made in your analysis of SCD total score might not be reasonable. We recommend that you conduct sensitivity analyses assuming missing not at random (MNAR). We also recommend sensitivity analyses using alternative variance covariance structures for the MMRM you proposed.**

- **Every subject should be accounted for in the analysis by either being measured for the primary endpoint or properly accounted for if not measured for the primary endpoint. The number of subjects not measured for an endpoint should be kept to a minimum. Too much missing data undermine the reliability and confidence of the results. Sensitivity analyses should be performed to account for the limitation of the data and to examine the potential impact of any missing data. For further advice on missing data see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials.**

Post-Meeting Comment:

For products seeking an indication for the treatment of a life-threatening disease, we recommend a primary endpoint be an objective measure of the disease. In this case, the addition of a symptom benefit claim can provide important supportive data of clinical benefit.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER

strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)

6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

See attached Sponsor handout/slides.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICOLE J GORMLEY
08/08/2016